

Paediatric renal transplantation in Northern Ireland (1984-1998)

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SUMMARY

Over the last 20 years a comprehensive paediatric nephrology service has been developed in Northern Ireland, based in the academic medical unit at the Royal Belfast Hospital for Sick Children (RBHSC). In the 15 years 1984-1998 a total of 77 renal transplants have taken place in patients aged 18 years and under. Initially transplants were only considered in children over five years of age but in the past eight years children as young as two years have successfully received kidneys. Aggressive nutritional support combined with peritoneal dialysis has enabled survival to a size when transplantation is feasible. The 5 year graft survival was 64%, with two children dying following transplantation. The complexity of managing this age group is reflected by the fact that a total of 10 transplants (13%) failed in the first 30 days. These figures compare favourably with statistics reported by similar paediatric centres from across the United Kingdom and Republic of Ireland, and with local results in adult patients. This demonstrates that a successful end stage renal replacement programme for children is achievable in a relatively small population, which is geographically isolated.

INTRODUCTION

Paediatric renal transplantation began in Northern Ireland in 1980. Despite clinical experience being limited by a relatively small population, long term graft and patient survival rates are comparable to other centres throughout the UK and Republic of Ireland. This represents a beneficial initial sharing of adult nephrology expertise with the paediatric team, and subsequent development of the ability to manage independently even the smallest child with renal failure.

METHODS AND PATIENTS

Data was provided by the United Kingdom Transplant Support Service Authority from the national transplant database. All patients 18 years and under at the time of renal transplantation in Northern Ireland between the years 1984 and 1998 inclusive were included. Information was collected relating to primary diagnosis, donor and recipient age, waiting time on the transplant list, organ refusal, graft and patient survival, cause of graft loss and growth parameters post transplant.

RESULTS

From 1984-1998 a total of 77 cadaveric renal transplants have taken place in Northern Ireland in patients 18 years of age and under. The commonest primary diagnosis was reflux nephropathy in 31 cases (40.3%), eight cases were caused by hereditary nephropathy (10.4%) and seven by glomerulonephritis (9%). Five (6.5%) cases were caused by congenital renal hypoplasia or dysplasia and one (1.3%) by each of the following – infantile polycystic kidney, medullary cystic disease, Alports disease and cystinosis. 22 cases were classified in the national transplant database as other diagnosis and not

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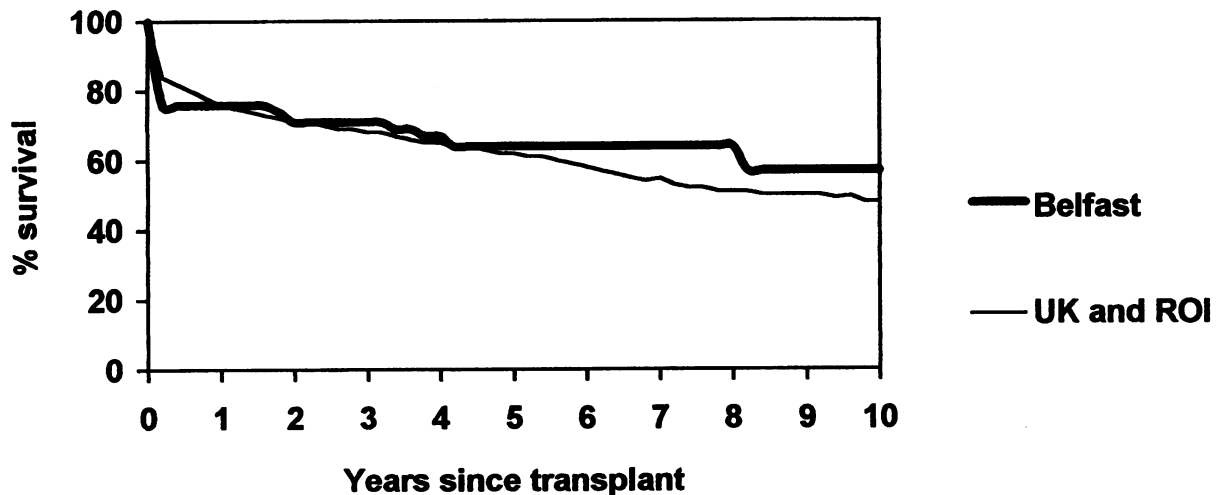


Fig 1. 10 year transplant survival plot for first cadaveric paediatric kidney grafts since 1984, Belfast v rest of UK and Republic of Ireland (ROI).

further specified. The five year graft survival was 64% (fig.1).

From 1984-1988 inclusive 15 donors (68% of donors for this 5 year period) to paediatric recipients were order then 18 years. In 1989-1993 10 donors (43% of donors for this 5 year period) and in 1994-1998 nine donors (28% of donors for this 5 year period) were adults. 23 donors in the period 1994-1998 (72% of donors for this 5 year period) were 18 years or less with 17 (53%) in the 5-14 age group.

In the period 1984-1990 all recipients were older than 5 years of age. From 1990-1998 nine transplants took place in the age group 2-4 years, none have taken place in recipients less than 2 years of age.

In 1984-1988 twenty-two patients waited on the transplant waiting list for a median time of 87 days, in 1989-1993 twenty five waited for a median time of 182 days and from 1994-1998 thirty patients waited a median time of 316 days for transplant.

One hundred and seventeen offers of organs were refused from 1984-1998. The commonest reason in 66 cases (56%) was an inadequate tissue match. Eight offers (6.8%) were rejected because the recipient was unfit, and eight because of lack of resources; 18 (15.4%) were not used because of problems related to donor age, size or history. In four (3.4%) cases the ischaemic time was unfavourable, a further four had associated adverse clinical factors. One (0.8%) was rejected for an anatomical reason, a further eight for reasons unspecified in the National Database.

Of the 77 transplants seven failed in the first 7 days post transplant and an additional three during days 8 to 30 (13%). Two deaths occurred in the early postoperative period (mortality rate of 2.6%). The causes were fluid overload and ARDS (acute respiratory distress disorder).

Of the children currently attending the RBHSC transplant follow-up clinic the mean standard deviation score for height is -0.83, with a range of -2.3 to +1.4. Only two children have a standard deviation score of less than -2.

DISCUSSION

Interest in transplantation dates back for centuries but the earliest experiments that met with any success occurred in the first decade of the last century. Kidneys that functioned briefly are recorded after transplantation from one dog to another by Ullman in 1902. By the fourth and fifth decades of the 20th century attempts were being made to transplant a kidney from a cadaver to a live recipient, but invariably met with failure. A breakthrough occurred in 1954 in Boston when an identical twin donated a kidney to his sibling and the graft survived for 8 years, failing because of recurrence of the primary disease.¹

In Belfast the first adult renal transplant which took place in 1962 between identical twins failed because of technical problems, but led to a successful haemodialysis and transplant programme for adults. A programme for children was inaugurated in 1980 with the appointment of a paediatric nephrologist and the introduction of a continuous peritoneal dialysis program using parent-operated automated cyclers. The service

is presently run by a multidisciplinary team led by 2 paediatric nephrologists (the second appointment being in 1995) supported by 3 renal nurse specialists, and a part time psychologist, dietician and social worker. All surgery is performed by renal transplant surgeons based at the Belfast City Hospital.

The United Kingdom Transplant Support Service Authority (UKTSSA) has recently published audit figures for renal transplants in the United Kingdom and Republic of Ireland for 1984-1993² and in this ten year period 1406 paediatric renal transplants (18 years and under) have taken place. Table I illustrates how Belfast compared with other centres on a numerical basis during this 10 year period.

In the 15 year period from 1984-1998 a total of 77 cadaveric renal transplants have taken place in Northern Ireland in patients under the age of 19 years. The 5 year graft survival of 64% compares favourably with nation-wide statistics (fig.1). 1990 was a particularly busy year (fig.2) when a total of 10 transplants took place supervised by a single paediatric nephrologist, with the active support of the adult nephrology team. The commonest primary diagnosis was reflux nephropathy, which explains the preoccupation of all paediatricians with the investigation of childhood urinary tract infections. There is the potential that some patients who present late in

TABLE I

Cadaveric kidney transplants in recipients aged 0-18 years at time of transplantation (1984-1993). (Population base ref. 14)

<i>Hospital</i>	<i>Number of Transplants</i>	<i>Population base (millions)</i>
Guys	238	9.13
Great Ormond		
Street/Royal Free	162	11.65
Manchester	132	4.0
Birmingham	117	5.49
Leeds	97	3.67
Dublin	83	4.5
Glasgow	79	5.1
Newcastle	65	3.03
Cardiff	58	2.16
Bristol	56	3.93
Belfast	47	1.59
Liverpool	26	3.06

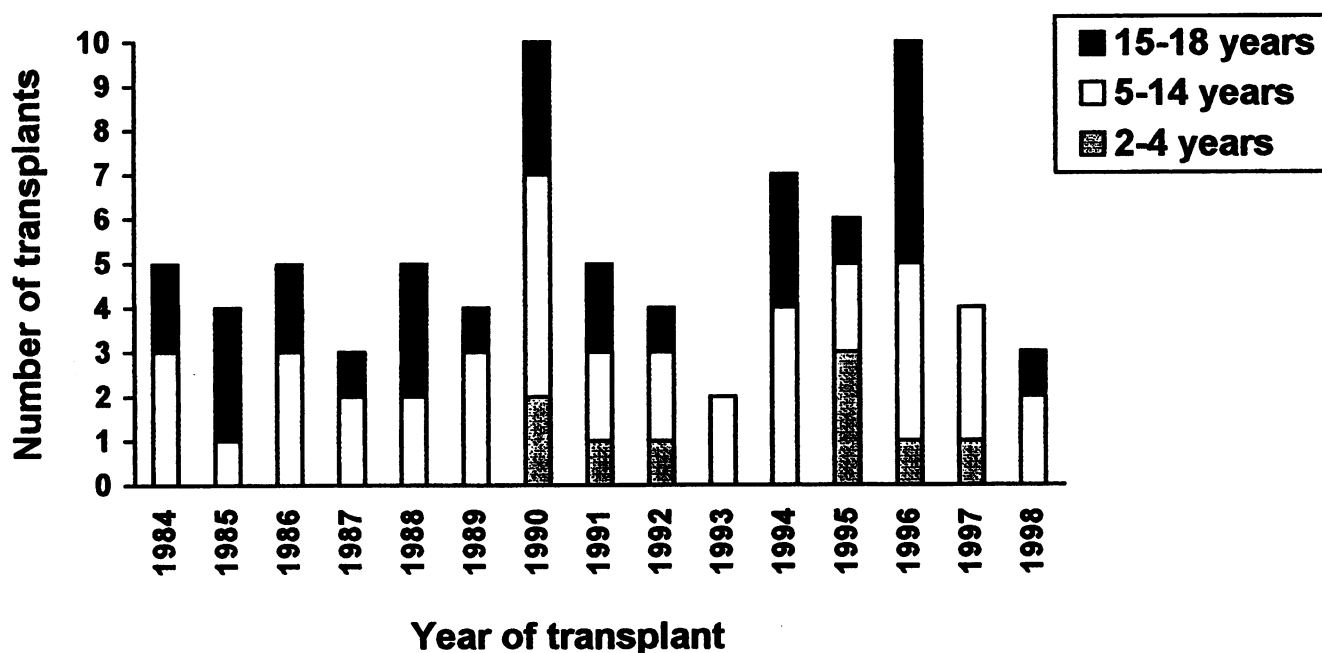


Fig 2. Paediatric cadaveric renal transplants in Belfast (1984-1998).

childhood with chronic pyelonephritis could be detected at an earlier phase by antenatal³ and family screening^{4,5} and early referral of children with proven urinary tract infections.^{6,7} Table II lists the other commonest causes which are very similar to the range of conditions encountered nation-wide. The Northern Ireland figures are obviously much smaller, and the apparent predominance of chronic pyelonephritis is not significant.

TABLE II

Primary renal disease leading to transplantation in 77 patients in Northern Ireland (1983-1998), compared with percentage figures for UK/Republic of Ireland (1984-1993).

<i>Primary renal disease</i>	<i>Total</i>	<i>Percentage of total (77)</i>	<i>Percentage of total in UK/ Republic of Ireland (1406)</i>
Glomerulonephritis	7	9%	12%
Pyelonephritis, chronic	31	40.3%	28%
Polycystic kidneys, infantile	1	1.3%	2%
Medullary cystic disease	1	1.3%	3%
Hereditary nephropathy	8	10.4%	1%
Alports syndrome	1	1.3%	1%
Cystinosis	1	1.3%	3%
Congenital renal hypoplasia	2	2.6%	6%
Congenital renal dysplasia +/- urinary tract malformation	3	3.9%	10%
Others	22	28.6%	34%

During the 15 year period the age range of the donors has been changing from a predominantly adult to a child population. This can be partly explained by the fact that in 1990 a new rule meant that a donated paediatric kidney was offered firstly to a paediatric patient. This change may also be partly explained by the increasing awareness of the medical profession and public alike of the need for organ donation, even when the potential donor is a dying child.

The age group of the recipient has also been changing during the 15 year period. Prior to 1990 all recipients were five years or older, but the 2-4 age group has seen an average of one transplant per year since then (figure 2). These nine transplants have become possible due to improving surgical techniques and because aggressive medical treatment of congenital nephrotic syndrome,⁸ and end-stage renal failure in neonates has enabled survival to a size and weight compatible with transplantation. A major contribution to patient-survival is the introduction of intensive skilled nutritional support including the use of night-time tube feeding via gastrostomy, and peritoneal dialysis techniques in infants as small as 1000 grams. The Paediatric team while having reservations about the developmental outcome of babies treated for chronic renal impairment from infancy, has demonstrated the ability to dialyse and transplant these infants.

The median waiting times on the transplant list have gradually increased in each successive 5 year period, initially being about 3 months but by the late 1990's extending to about 11 months. This of course is not a problem unique to Northern Ireland. Despite national publicity campaigns organ demand continues to outstrip donation. Live donation is an alternative which has been underway for decades; locally a total of 5 such donations have taken place, 3 of which are still functioning.

Generally only a kidney with a haplotype tissue type match is considered and ideally a match on both DR loci is sought. Not every kidney offered therefore will be accepted, and on average 8 were turned down each year. Figure 3 shows that, as expected, the commonest reason by far is that a better match was required. Other factors to be considered include a prolonged ischaemic time (>24 hours) or adverse anatomical reasons e.g. in one case a tear in the renal vein meant that the operation would be technically difficult. It is unfortunate that 8 offers had to be declined because of lack of resources. In practice this usually meant the lack of a post-operative intensive-care bed or that key consultant nephrology or surgical staff were not available. This is a problem that is seen throughout the UK and Republic of Ireland where about 4% of offers are turned down for this reason.²

Of the 77 paediatric transplants in Belfast we have seen seven fail in the first 7 days post-

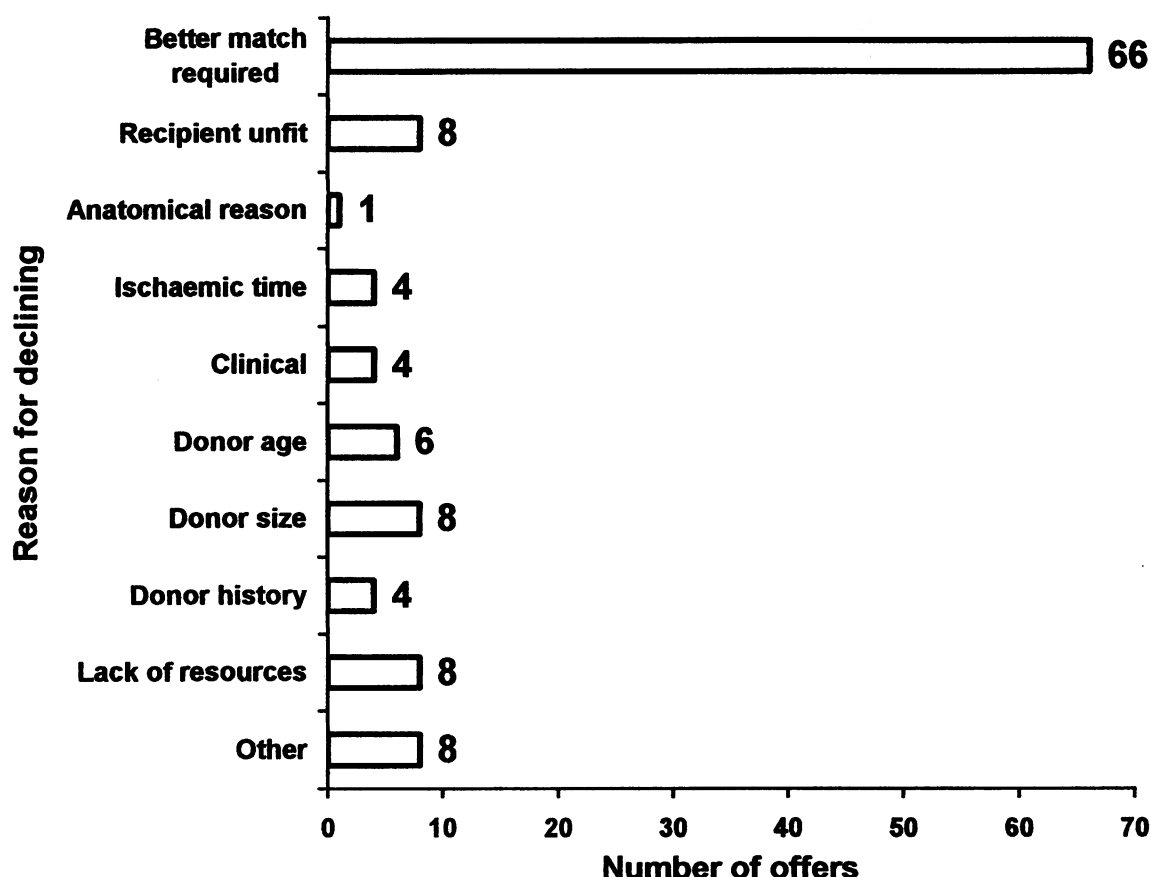


Fig 3. Reasons for declining paediatric kidney offers to Belfast (1984-1998).

transplant and an additional three in days 8 to 30, amounting to 13%. Guy's hospital for example has seen 45 fail in the first 30 days post transplant² accounting for 19% of the total (these statistics cover the period 1983-1994). The classifications of causes of graft failure shown in Table III are those employed by the UK Transplant Support Service. Initially a proportion of kidneys may be lost immediately following surgical placement due to an overwhelming immunological reaction. These are classified under the general title of hyperacute rejection. We believe this grouping fails to distinguish in our patients between severe immunological rejection, and early vascular thrombosis possibly caused by technical problems with the anastomosis. In 10% the primary cause of renal failure has recurred, usually glomerulonephritis. The apparent difference in the proportion of local patients suffering from rejection whilst on immunosuppression compared to nationwide figures, (Table III) is likely on review to result from a local anomaly in data reporting. The Belfast graft losses on immunosuppression are probably similar but hidden within the "other" category.

Two deaths, both occurring in the early postoperative period, represent a mortality rate of 2.6%. The causes of death were (a) fluid overload and (b) ARDS (Acute Respiratory Distress Syndrome.) In the UK and Republic of Ireland 48 deaths occurred in the 10 year period 1984-1993 giving a mortality rate of 3.4%, the 4 commonest causes of death being cardiac arrest (15%), fluid overload (13%), pulmonary infection (10%) and septicaemia (8%).² An ongoing audit of causes of early graft loss and death has led to refinement of transplant protocols in order to improve outcome.

Initially all children were immunosuppressed with prednisolone and azathioprine in combination until the mid 1980's. When cyclosporin became available it was an important milestone, which led to improved graft survival.⁹ This drug works by inhibiting the transcription of interleukin 2 and thus early T cell activation. The use of cyclosporin became routine in our children despite initial dosage difficulties related to variable metabolism in childhood. Nephrotoxicity is avoided by careful blood level monitoring but

TABLE III

Cause of graft failure in Northern Ireland, (1984-1998), compared to graft failure in the UK/Republic of Ireland (1984-1993).

<i>Cause of failure</i>	<i>Northern Ireland</i>	<i>UK/ Republic of Ireland</i>
Hyperacute rejection	14%	2%
Rejection while on immunosuppressive drugs	29%	67%
Recurrent primary renal disease	10%	3%
Vascular or ureteric operative problems	5%	8%
Vascular thrombosis	19%	12%
Other	23%	8%

side-effects causing persistent and occasionally unacceptable problems are hirsutism and gum hypertrophy. More recently Tacrolimus, (a macrolide antibiotic) an agent with immunosuppressive activity approximately 100 times that of cyclosporin,¹⁰ has become established as an efficacious drug in this field in which side-effects (e.g. nephrotoxicity and neurotoxicity) are reversible with dosage reduction.¹¹

Of the children currently attending the RBHSC transplant follow-up clinic the mean standard deviation score for height is -0.83, with a range of -2.3 to +1.4. Only two children have a standard deviation score of less than -2, both of whom have been in chronic renal failure since infancy. This reflects careful attention to renal bone disease (using phosphate binders and vitamin D analogues), nutrition and the use of human growth hormone¹² in these children, and is one of the most dramatic improvements in this age group. Eradication of short stature as a result of chronic renal impairment and renal osteodystrophy is potentially achievable in all patients who can comply with modern treatment regimens.

CONCLUSION

Our figures demonstrate that in terms of short and long term graft survival and mortality Belfast is comparable to any similar centre nation-wide. Advances have been made during the 15 year period, most noticeably in the youngest children receiving transplantation. It is clear that a

successful end stage renal replacement programme for children is achievable in a small geographical area with a limited population. There are advantages of an association with an adult unit, but the special needs of chronically ill children and demands for professional family support require the skills of a paediatric medical environment. Concerns for the future must focus on the ever-increasing waiting time and the shortage of donated organs, which are not problems restricted to Northern Ireland. Living related donation is part of the solution, and of course xenotransplantation may prove to be a controversial solution in the 21st century and is at present being evaluated.¹³

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